11. [Amended] The method of claim [9] 8, wherein the therapeutic agent is injected into the tumor.

15. [Amended] The method of claim 8, wherein the antisense nucleic acid sequence is [phosphothiolated] phosphorothiolated.

18. [Amended] The method of claim 8, wherein the antisense nucleic acid sequence is complementary to 90% [identical to] of the nucleic acid encoding an antioxidant enzyme.

19. [Amended] The method of claim 8, wherein the antisense nucleic acid sequence is complementary to 100% [identical to] of the nucleic acid encoding an antioxidant enzyme.

20. [New] An oligonucleotide comprising an antisense nucleic acid sequence that specifically binds to a nucleic acid encoding an antioxidant enzyme start codon, wherein the sequence is SEQ ID NO:1, 2 or 3.

21. [New] The oligonucleotide of claim 20, wherein the antisense nucleic acid sequence is phosphorothiolated.

REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on June 18, 2002, and the references cited therewith.

Claims 1-3, 5-8, 11, 15, 18 and 19 are amended, claims 4, 9 and 10 are canceled, and claims 20 and 21 are newly added; as a result, claims 1-3, 5-8 and 11-21 are now pending in this application.

The amendments to the claims have been made to expedite prosecution of the present application. The amendments to the claims are fully supported by the specification as originally filed, and no new subject matter has been added.

The amendment to claim 1 to add "a nucleic acid encoding" is supported by the originally-filed specification, for example, by page 3, lines 16-18, and the Sequence Listing. Claim 1 has also been amended to recite the enzymes listed in original claim 4. The amendment to claims 2, 3, 6, 7 15, 18 and 19 have been made simply to clarify that the claims are referring to the antisense nucleic acid sequence.

Claims 3 and 15 have been amended to correct typographical errors.

Claims 6, 7, 18 and 19 have been amended to clarify that the antisense nucleic acid sequence is complementary to the nucleic acid encoding an antioxidant enzyme. Support for this amendment is found in the specification, for example, by page 3, lines 16-18.

Claim 8 has been amended to clarify that the antioxidant enzyme malfunction disorder is a tumor. Support for this amendment is found in original claim 10. Claim 8 has also been amended to recite the features of original claim 1.

Claim 11 has been amended to depend from claim 8.

Support for new claims 20 and 21 can be found, for example, on page 4, lines 7-13 of the specification, the Sequence Listing, and original claim 3.

§112 Rejections of the Claims

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-19 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The examiner has stated that claims 1, and 2-19 which follow from it, are indefinite since the term "antioxidant enzyme" is a protein, and thus does not have a start codon. Claim 1 has been amended to clarify that the antisense oligonucleotide specifically binds to a nucleic acid encoding an antioxidant enzyme start codon, and not to a protein.

The examiner stated that claims 2 and 3 were indefinite, in that it was not clear which nucleic acid sequence is 20 nucleotides long or is phosphorothiolated. These claims have been amended to clarify that it is the antisense oligonucleotide that is 20 nucleotides long or is phosphorothiolated.

The examiner stated that claims 6, 7, 18 and 19 are indefinite in reciting that the nucleic acid sequence is identical to the nucleic acid encoding an antioxidant enzyme. These claims have been amended to recite that the antisense sequence is complementary to the nucleic acid encoding an antioxidant enzyme.

Applicant requests that these rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph – Written Description

Claims 1-19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains that the inventor at the time the application was filed, had possession of the claimed invention (written description). In particular, the examiner stated that "the claims are drawn broadly to encompass the genus of all antioxidant enzymes, or said subset of antioxidant enzymes, or to human superoxide dismutase, which includes all orthologs, splice variants and alleles thereof," and that written description is provided only for human superoxide dismutase (SEQ ID NO: 11).

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. M.P.E.P. § 2163.I.A (citing *In re Wertheim*, 541 F.2d 257, 263 191 USPQ 90,97 (C.C.P.A. 1976)). Rejection of an original claim for lack of written description should be rare. M.P.E.P. § 2163.II.A (inquiry is primarily factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure). What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. M.P.E.P. § 2163.II.A.3(a) (citing to *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986)). An inventor is not required to describe every detail of the invention.

Further, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or

disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. M.P.E.P. § 2163.II.A.3(a)(ii).

Applicant asserts that at the time the application was filed, several other antioxidant enzymes were known (*e.g.*, copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase). These antioxidant enzymes were specifically listed on page 1, lines 28-30, in addition to being included in original claim 4. Because these enzymes were known at the time of filing, one of skill in the art would have been able to make the claimed antisense oligonucleotides, given the teaching of the present invention. Further, at page 3, line 27 through page 4, line 27, the specification provides oligonucleotide constructs that bind to the coding sequences of catalase and phospholipid glutathione peroxidase. Applicant, therefore, has specifically described at least two oligonucleotide sequences that bind to nucleic acids encoding three different antioxidant enzymes, specifically manganese superoxide dismutase, catalase, and phospholipid glutathione peroxidase (*i.e.*, a total of seven oligonucleotides were specifically included in the specification -- SEQ ID NOs: 1-3 (manganese superoxide dismutase, catalase), SEQ ID NOs: 4-5 (catalase), and SEQ ID NOs: 6-7 (phospholipid glutathione peroxidase)). Applicant, therefore, has provided a written description of the claimed genus.

Regarding the examiner's statement that "the claims are drawn broadly to encompass the genus of all antioxidant enzymes, or said subset of antioxidant enzymes, or to human superoxide dismutase, which includes all orthologs, splice variants and alleles thereof." Applicant respectfully reminds the examiner that the claims recite an antisense nucleic acid sequence. Applicant is not claiming antioxidant enzymes. The claims recite antisense oligonucleotides where the antisense nucleic acid sequences specifically bind to nucleic acids encoding antioxidant enzyme start codons, wherein the sequence of each antisense oligonucleotide is about 18 to 26 nucleotides in length. Thus, the claimed oligonucleotide has specific structure and function: structurally it is a nucleic acid sequence that is about 18 to 26 nucleotides in length, and functionally it binds to a nucleic acid encoding an antioxidant enzyme start codon.

Thus, Applicant has provided adequate written description for the pending claims. Applicant requests that this rejection under 35 U.S.C. § 112, first paragraph (written description) be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph – Scope of Enablement

Claims 8, 9, and 11-19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention (scope of enablement). Claim 10 was free of this rejection.

The examiner has indicated at page 6 of the June 18, 2002 Office Action that the specification is enabled for *in vivo* antisense-mediated inhibition of human superoxide dismutase in the treatment of tumors. Independent claim 8 has been amended to recite that the disorder is a tumor as recited in original claim 10. Applicant requests that this rejection under 35 U.S.C. § 112, first paragraph (enablement) be withdrawn.

§102 Rejection of the Claims

Claims 1-7 were rejected under 35 U.S.C. § 102(b) as being anticipated by Gonzalez-Zulueta et al. (1998) *J. Neurosci.* 18(6) 2040-2055.

The examiner states that Gonzalez-Zulueta *et al.* teach a phosphorothiolated antisense compound that targets the start codon of human manganese superoxide dismutase and is 19 nucleotides long. With all due respect, the examiner is in error that Gonzalez-Zulueta *et al.* disclose a human MnSOD. Gonzalez-Zulueta *et al.* instead used only rat MnSOD with rat cells. The claims have now been amended to recite oligonucleotides that bind to nucleic acids encoding copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase (claim 1), and oligonucleotides of SEQ ID NO:1, 2, and 3 (claim 20). Gonzalez-Zulueta *et al.* do not teach or suggest any of these oligonucleotides. Therefore, this rejection under 35 U.S.C. § 102(b) should be withdrawn.

Information Disclosure Statement

Attached is a copy of Applicant's 2-page Form 1449, filed with an Information Disclosure Statement dated May 22, 2002, which was partially initialled and returned with the Examiner's Office Action mailed June 18, 2002. On page 2 of the 1449 form, the Examiner has apparently overlooked initialling the first reference, Biocemistry [sic] and Biophysics, 352 (1), (1998), pp. 51-58. It is respectfully requested that this reference be initialled, and the form returned with the Examiner's next action.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 C.F.R. 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 11 day of October, 2002.

Candis B. Buending
Name

Candis B. Buending
Signature

CLEAN VERSION OF CLAIMS

1. [Amended] An oligonucleotide comprising an antisense nucleic acid sequence that specifically binds to a nucleic acid encoding an antioxidant enzyme start codon, wherein the antisense sequence is about 18 to 26 nucleotides in length, and wherein the antioxidant enzyme is copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase.

A1

2. [Amended] The oligonucleotide of claim 1, wherein the antisense nucleic acid is about 20 nucleotides in length.

3. [Amended] The oligonucleotide of claim 1, wherein the antisense nucleic acid sequence is phosphorothiolated.

5. [Amended] The oligonucleotide of claim 4, wherein the antioxidant enzyme is catalase or phospholipid glutathione peroxidase.

6. [Amended] The oligonucleotide of claim 1, wherein the antisense nucleic acid sequence is complementary to 90% of the nucleic acid encoding an antioxidant enzyme.

A2

7. [Amended] The oligonucleotide of claim 1, wherein the antisense nucleic acid sequence is complementary to 100% of the nucleic acid encoding an antioxidant enzyme.

8. [Amended] A method of treating a tumor in a mammal comprising reducing antioxidant enzyme levels in a cell by administering a therapeutic agent comprising an antisense nucleic acid sequence that specifically binds to a nucleic acid encoding an antioxidant enzyme start codon, wherein the antisense sequence is about 18 to 26 nucleotides in length.

A3

11. [Amended] The method of claim 8, wherein the therapeutic agent is injected into the tumor.

12. The method of claim 8, wherein the mammal is a human.

N.E.

13. The method of claim 8, wherein the therapeutic agent further comprises a delivery vehicle.

14. The method of claim 13, wherein the delivery vehicle is lipofectamine or –[1-(2,3-dioleoyloxy)propyl]-*N,N,N*-trimethylammonium methyl sulfate ("DOTAP").

A4

15. [Amended] The method of claim 8, wherein the antisense nucleic acid sequence is phosphorothiolated.

N.E.

16. The method of claim 8, wherein the antioxidant enzyme is manganese superoxide dismutase, copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase.

17. The method of claim 16, wherein the antioxidant enzyme is manganese superoxide dismutase, catalase, or phospholipid glutathione peroxidase.

A5

18. [Amended] The method of claim 8, wherein the antisense nucleic acid sequence is complementary to 90% of the nucleic acid encoding an antioxidant enzyme.

19. [Amended] The method of claim 8, wherein the antisense nucleic acid sequence is complementary to 100% of the nucleic acid encoding an antioxidant enzyme.

20. [New] An oligonucleotide comprising an antisense nucleic acid sequence that specifically binds to a nucleic acid encoding an antioxidant enzyme start codon, wherein the sequence is SEQ ID NO:1, 2 or 3.

A6

21. [New] The oligonucleotide of claim 20, wherein the antisense nucleic acid sequence is phosphorothiolated.